Support for the amendments and new claims can be found throughout the specification and in the claims as filed. In particular, support for the amendment to claims 56 and 74 can be found, for example, on page 8, lines 17-28; page 16, line 30, to page 17, line 14; page 28, line 20, to page 29, line 19; and page 42, line 29, to page 43, line 5. Support for new claims 105 and 106 can be found, for example, on page 17, lines 3-9. Support for new claim 107 can be found, for example, in original claims 56, 60-65, 69 and 73 and on page 8, lines 17-28; page 16, line 30, to page 17, line 14; page 28, line 20, to page 29, line 19; and page 42, line 29, to page 43, line 5. Support for new claim 108 can be found in original claims 74 and 77 and on page 8, lines 17-28; page 16, line 30, to page 17, line 14; page 28, line 20, to page 29, line 19; and page 42, line 29, to page 43, line 5. Support for new claims 109-128 can be found, for example, in the claims as filed and on page 39, line 17, to page 45, line 24. Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested. Entry of the proposed amendments and new claims is respectfully submitted to be proper because the amendments are believed to place the claims in condition for allowance.

Applicant has set forth above the amendment to the claims in clean form. Applicant also attaches Appendix A with marked up amendments indicated with brackets and underlining.

In addition to co-pending application serial Nos. 08/791,391 and 08/790,540, Applicant brings to the Examiner's attention co-pending application serial No. 09/339,922.

Formal Drawings

The Office Action indicates on page 2 that formal drawings were submitted that did not comply with 37 C.F.R. § 1.84. Applicant respectfully points out that the figures submitted with the application were informal drawings. However, submitted herewith are formal drawings which are believed to satisfy the requirements of 37 C.F.R. § 1.84.

Regarding Claims Reciting SEQ ID NOS

New claims 107-110 have been added, which recite a Markush group of CDRs having specifically recited SEQ ID NOS. Claims 60-65, 69, 73 and 77 have been amended to depend from claim 107. Claims 80, 82, 84, 86, 88, 90, 92, 94 and 96 have been amended to depend from claim 109. New claims 111-128 are dependent claims of claim 110.

Applicant appreciates the Examiner's invitation on page 10, section 14, of the Office Action and respectfully submits that new claim 110, and dependent claims 111-128, are directed to $\alpha_V\beta_3$-specific antibodies comprising SEQ ID NOS indicated to be free of the prior art. Applicant notes that, of the SEQ ID NOS indicated to be free of the prior art on page 10, section 14, SEQ ID NO: 66 is not included. Applicant believes that SEQ ID NO:66 is also free of the prior art.

As requested in the Office Action mailed November 24, 1999, regarding the election of species, Applicant points out that new claims 107-110, 115, 116 and 121-128 are

readable on the elected species of SEQ ID NOS:90 and 94, as elected in the response mailed April 24, 2000. Applicant also points to section 7 of the Office Action mailed November 24, 1999, which indicates that upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. Applicant respectfully submits that, based on the amendments and new claims and for the reasons set forth below, generic claims 107-110 are allowable. Accordingly, Applicant respectfully requests consideration of claims to additional species reciting SEQ ID NOS, in addition to elected species SEQ ID NOS:90 and 94.

For the convenience of the Examiner, Applicant sets forth below the relationship of the claims upon entry of the amendment:

Independent Claim	Dependent Claims
Claim 56	Claims 57-59, 66-68, 70-72
Claim 74	Claims 75-76
Claim 107	Claims 60-65, 69, 73
Claim 108	Claim 77
Claim 109	Claims 80-97
Claim 110	Claims 111-128

Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 under 35 U.S.C. § 112, first paragraph, as

allegedly lacking written description is respectfully traversed. The Office Action alleges that the specification does not provide support for the phrase "one or more CDR's having."

Applicant respectfully maintains that the specification provides sufficient written description for the phrase "one or more CDRs," as recited in claims 56 and 74. Support for the phrase "one or more CDRs" can be found, for example, in original claims 56 and 74 and on page 41, line 3, to page 42, line 2, page 43, lines 5-12, and page 44, lines 11-15. The specification teaches that an enhanced LM609 grafted antibody includes those containing "at least one of the following CDRs having single amino acid substitutions," followed by 23 exemplary CDR sequences (page 41, line 5, to page 42, line 2). The specification also teaches that an enhanced LM609 grafted antibody can contain "at least one of the following CDRs containing multiple amino acid substitutions," followed by four exemplary CDR sequences (page 43, lines 5-12). The specification additionally teaches that an enhanced LM609 grafted antibody can have at least one CDR having two or more amino acid substitutions (page 44, lines 11-15). Applicant respectfully submits that the phrase "one or more CDRs having at least one amino acid substitution" is supported by the teachings in the specification of "at least one of the following CDRs having single amino acid substitutions" as well as the 27 exemplary CDR sequences having such characteristics. Accordingly, Applicant respectfully submits that the specification provides sufficient description and guidance for the phrase "one or more CDRs having" and respectfully requests that this rejection be withdrawn.

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The rejection of claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Office Action maintains that the LM609 antibody is required to practice the claimed invention.

Applicant maintains that the specification provides sufficient description and guidance to enable those skilled in the art to practice the invention as claimed. Regarding the alleged requirement to deposit the hybridoma producing LM609 hybridoma, 37 C.F.R. § 1.802(b) states that biological material need not be deposited if it is known and readily available to the public or can be made or isolated without undue experimentation. Applicant respectfully maintains that the specification provides sufficient description and guidance such that one skilled in the art could make the claimed antibodies without undue experimentation. The nucleotide sequence and deduced amino acid sequence of LM609 heavy chain variable region (SEQ ID NOS: 5 and 6, respectively) and LM609 light chain variable region (SEQ ID NOS:7 and 8, respectively) are disclosed in the specification (see Figure 2 and page 6, lines 1-10). Furthermore, the specification teaches methods of grafting LM609 CDRs (page 17, line 24, to page 18, line 20; page 19, lines 1-17; page 22, line 30, to page 23, line 24; page 35, line 10, to page 36, line 2; and Example V, pages 77-82). The claims are directed to grafted antibodies containing LM609 CDRs having at least one amino acid substitution in one or more CDRs. Accordingly, it is the sequence of LM609 CDRs and substituted LM609 CDRs, which are disclosed in the specification, that are required to practice the claimed invention, not the sequence of the entire LM609 antibody.

Using the disclosed nucleotide sequences of the LM609 heavy and light chain variable regions, which provide antibody specificity, one skilled in the art can readily obtain an LM609 grafted antibody or functional fragment thereof using methods well known in the art. Thus, the disclosure of the nucleotide sequence of the LM609 heavy and light chain variable regions is all that is necessary to practice the invention as claimed. Therefore, the rejection of claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 is respectfully requested to be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed.

The Office Action indicates that claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are indefinite for the phrase "enhanced LM609 grafted antibody." Regarding claims 74-76, claim 74 does not recite the phrase "enhanced LM609 grafted antibody." Claim 74 has also been amended to delete the term "enhanced." Regarding claim 77, this claim has been amended to depend from new claim 108, which recites a Markush group of SEQ ID NOS, and the phrase "enhanced LM609 grafted antibody" is not recited in these claims. Regarding claims 84, 85, 90, 91 and 94-97, these claims have been amended to depend from new claim 109, and the phrase "enhanced LM609 grafted antibody" is not recited in claim 109 or these cited claims. Accordingly, since the phrase "enhanced LM609 grafted antibody" is not recited in claims 74-77, 84, 85, 90, 91 and 94-97, Applicant respectfully

requests that the rejection of these claims be withdrawn. Furthermore, the phrase "enhanced LM609 grafted antibody" is not recited in new claims 108-128.

Regarding the phrase "enhanced LM609 grafted antibody," Applicant maintains that this phrase is clear and definite. In regard to the term "enhanced," the specification teaches that an enhanced antibody is one in which a functional characteristic of the antibody has been altered or augmented compared to a reference antibody so that the antibody exhibits a desirable property or activity (see page 16, line 30, to page 17, line 14). Exemplary enhanced activity includes higher or lower affinity, increased or decreased association or dissociation rates, or increased stability compared to a reference antibody such as the LM609 grafted parent antibody (page 17, lines 3-14). Therefore, it is respectfully submitted that the meaning of the term "enhanced" is clear in view of the teachings in the specification.

Furthermore, claim 56, as amended, recites specific structural and functional characteristics of the claimed enhanced LM609 grafted antibody. In particular, the claim recites that the binding affinity of the enhanced LM609 grafted antibody is maintained relative to parental LM609 grafted antibody. Applicant therefore respectfully submits that claim 56, and dependent claims 57-59, are clear and definite.

Regarding claims new claim 107, which is directed to an enhanced LM609 grafted antibody having specifically recited CDRs, the claim recites that the binding affinity of the enhanced LM609

grafted antibody is maintained relative to parental LM609 grafted antibody. Therefore, Applicant respectfully submits that the claim recites specific functional characteristics of the claimed enhanced LM609 grafted antibodies. Applicant also points out that claims 60-65, 69 and 73 were amended to depend from claim 107.

The Office Action asserts on page 5, paragraph 5, that the claimed enhanced LM609 antibody can have contrasting properties and still be considered enhanced with respect to the reference LM609. As described above, Applicant points out that the claims recite functional characteristics of the claimed enhanced LM609 grafted antibodies. In particular, claims 56 and 107 recite that the $\alpha_v\beta_3$ binding affinity of the enhanced LM609 grafted antibody is maintained relative to parental LM609 grafted antibody. Thus, claim 56, and dependent claims 57-59, 66-68 and 70-72, and claim 107, and dependent claims 60-65, 69 and 73, recite specific functional characteristics of the claimed enhanced LM609 grafted antibody, that the binding affinity is maintained relative to parental LM609 grafted antibody. Applicant also points out that claim 74, although it does not recite the phrase "enhanced LM609 grafted antibody," recites specific functional characteristics of the claimed high affinity LM609 grafted antibody, that the binding affinity is higher affinity relative to parental LM609 grafted antibody. Therefore, Applicant respectfully submits that the characteristics of the claimed enhanced LM609 grafted antibody or high affinity LM609 grafted antibody are specifically recited in the claims.

Applicant respectfully submits that the claims reciting the phrase "enhanced LM609 grafted antibody," claims 56-73, are clear and definite. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 stand rejected as allegedly indefinite for the term "LM609." In this regard, Applicant points out that the term "LM609" is not recited in claims 84, 85, 90, 91 and 94-97. Furthermore, new claim 109, from which these claims have been amended to depend from, also does not recite the term "LM609." Accordingly, Applicant respectfully requests that the rejection of claims 84, 85, 90, 91 and 94-97 as allegedly indefinite for the term "LM609" be withdrawn.

Regarding claims reciting "LM609," Applicant maintains that the claims reciting this term are clear and definite. In particular, the claims reciting LM609 also recite specific structural and functional characteristics. Specifically, the claims reciting LM609 also recite that the antibody or functional fragment has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Additionally, the claims recite structural characteristics of the claimed grafted antibodies as it relates to LM609, in particular the CDRs of the LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or the LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8. Therefore, Applicant maintains that the claims reciting the term "LM609" are clear and definite.

Applicant respectfully disagrees with the assertion in the Office Action on page 5, section B, that the entire LM609 antibody sequence or deposit of the LM609 hybridoma is required to practice the claimed invention. The claims are directed to grafted antibodies containing LM609 CDRs having at least one amino acid substitution in one or more CDRs. For the reasons described above, it is the sequence of LM609 CDRs and substituted LM609 CDRs, which are disclosed in the specification, that are required to practice the claimed invention, not the sequence of the entire LM609 antibody. Using the disclosed nucleotide sequences of the LM609 heavy and light chain variable regions, which provide antibody specificity, one skilled in the art can readily obtain an LM609 grafted antibody or functional fragment thereof using methods described in the specification and well known in the art. Thus, the disclosure of the nucleotide sequence of the LM609 heavy and light chain variable regions is all that is necessary to practice the invention as claimed. Furthermore, in light of the specific structural and functional characteristics of the claimed grafted antibodies, including characteristics of LM609 relevant to the claimed grafted antibodies, Applicant respectfully maintains that the claims reciting LM609 are clear and definite. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(e)

The rejection of claims 56-59, 62, 65-68, 70-75, 77, 84, 85, 90, 91 and 94-97 under 35 U.S.C. § 102(e) as allegedly anticipated by Brooks et al., U.S. Patent No. 5,753,230, is respectfully traversed. The Office Action indicates that, since

the prior art teaches humanized LM609 antibodies and that the claimed "enhanced LM609 antibody" encompasses a variety of modified forms of LM609, the prior art humanized antibodies read on the claimed antibodies.

Applicant maintains that the claimed grafted antibodies are novel over Brooks et al. Applicant points out that claims 84, 85, 90, 91 and 94-97 do not recite the phrase "enhanced LM609 antibody." Regarding the claims reciting the phrase "enhanced LM609 antibody," Applicant maintains that Brooks et al. does not teach the claimed grafted antibodies. The claims are directed to grafted antibodies having at least one amino acid substitution in one or more CDRs of a LM609 grafted antibody. In particular, claim 56 is directed to an enhanced LM609 grafted antibody exhibiting selective binding affinity to $\alpha_v\beta_3$, or a functional fragment thereof, comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, the antibody or functional fragment thereof having integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity, wherein the $\alpha_v\beta_3$ binding affinity of the enhanced LM609 grafted antibody is maintained relative to parental LM609 grafted antibody. Claim 62 recites specific SEQ ID NOS of CDRs having at least one amino acid substitution.

To anticipate a claim, the reference must teach every element of the claim. Anticipation requires the disclosure in a single prior art reference of each element of the claim under

consideration. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989); In re Spada, 15 U.S.P.Q.2d 1655 (Fed. Cir. 1990). "[A]ll limitations in the claims must be found in the reference since the claims measure the invention." In re Lange, 644 F.2d 856, 862, 209 U.S.P.Q. 288, 293 (C.C.P.A. 1981).

In contrast to the claimed grafted antibodies, Brooks et al. does not teach the claimed grafted antibodies having one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted antibody. Furthermore, Brooks et al. does not teach any of the structural features of LM609, let alone the claimed CDRs having at least one amino acid substitution. Moreover, Brooks et al. provides no teachings of substituting an amino acid in a LM609 CDR, as in Applicant's claimed grafted antibodies. Thus, Brooks et al. does not teach every element of the claimed invention. Accordingly, absent a teaching of every element of the claimed invention, Applicant respectfully submits that Brooks et al. cannot anticipate the claims. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 103

The rejection of claims 56-59, 62, 66-68, 70, 71 and 74-76 under 35 U.S.C. § 103 as allegedly obvious over Brooks et al., U.S. Patent No. 5,753,230, in view of know art for gene cloning and expression strategies for deriving recombinant antibodies is respectfully traversed. Applicant respectfully submits that the claimed grafted antibodies are unobvious over Brooks et al., alone or in view of known methods of gene cloning

and expression strategies.

In contrast to Applicant's claimed invention, Brooks et al. does not teach or suggest an enhanced LM609 grafted antibody exhibiting selective binding affinity to $\alpha_v\beta_3$, or a functional fragment thereof, comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, the antibody or functional fragment thereof having integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity, wherein the $\alpha_v\beta_3$ binding affinity of the enhanced LM609 grafted antibody is maintained relative to parental LM609 grafted antibody, as recited in claim 56. Furthermore, Brooks et al. does not teach the specifically recited CDRs having at least one amino acid substitution in a LM609 grafted antibody heavy or light chain variable region CDR.

Applicant submits that Brooks et al., alone or in combination with known methods of gene cloning or any of the references Queen et al. (U.S. Patent No. 5,585,089), Rosok et al. (J. Biol. Chem. 271:22611-22618 (12996)), or Glaser et al. (J. Immunol. 149:3903-3913 (1992)), does not teach or suggest all the elements of the claimed grafted antibodies. First, Brooks et al. does not teach or suggest structural characteristics of LM609, as recited in claim 56. Second, Brooks et al. does not teach or suggest substituting an amino acid in a CDR of LM609, let alone the structural characteristics of LM609 CDRs having at least one amino acid substitution that are specifically recited in the

claims. Therefore, Brooks et al., alone or in combination with known methods of gene cloning, does not teach or suggest every element of the claimed invention. Absent such a teaching or suggestion, Applicant maintains that the claimed grafted antibodies are unobvious over Brooks et al., alone or in combination with known methods of gene cloning. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Provisional Double Patenting Rejection

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-18 and 26-31 of copending application serial No. 08/790,540 and claims 1-8, 15-26 and 33-42 of copending application serial No. 08/791,391. The Office Action indicates that, although the conflicting claims are not identical, they are not patentably distinct from each other because each application is drawn to the same or nearly the same LM609-specific antibodies and nucleic acids encoding the antibodies and modifications thereof.

Applicant respectfully submits that the claimed enhanced LM609 grafted antibodies are patentably distinct from the claims in either of copending application serial Nos. 08/790,540 or 08/791,391. The claims in either of application serial Nos. 08/790,540 or 08/791,391 are not directed to an enhanced LM609 grafted antibody comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide

referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, as claimed in the subject application. Furthermore, the claims of application serial Nos. 08/790,540 or 08/791,391 are not directed to the claims reciting SEQ ID NOS of CDRs having at least one amino acid substitution. Therefore, Applicant maintains that the claims of the present application are unobvious over the claims of application serial Nos. 08/790,540 or 08/791,391. Accordingly, Applicant respectfully requests that the provisional double patenting rejection be withdrawn.

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 are alleged to be directed to an invention not patentably distinct from claims 1-18 and 26-31 of copending application serial No. 08/790,540. The Office Action states that the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in the instant application was made or to name the prior inventor of the conflicting subject matter. Applicant respectfully requests that this requirement be held in abeyance until there is an indication of allowable subject matter.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The

Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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